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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/109,119	06/30/98	BOLDT	B GTIBEN.001

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EXAMINER	
GOLDBERG, I	
ART UNIT	**PAPER NUMBER**
1655	14

DATE MAILED: 07/31/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/109,119	Applicant(s) BOLDT ET AL.	
	Examiner Jeanine A Enewold Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2000*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This action is in response to the papers filed June 28, 2001. Currently, claims 1-20 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection necessitated by amendment.

4. This action is FINAL.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Urdea (US Pat. 5,200,314, April 1993).

Urdea teaches a kit which comprises a probe, a support, primers specific for an analyte polynucleotide, a labeled probe, DNA polymerase, a denaturation reagent for denaturing the analyte (col. 11-12). Thus, Urdea has taught every limitation of the instant claims.

Response to Arguments

The response states that Claims 1-20 have been rejected as being anticipated by Newton et al., and other prior art, but does not address Urdea. The response provides no arguments directed to the kits of Claims 17-20. Applicants have asserts that they believe the rejections have been obviated and that claims 1-16 are believed to be allowable. However, the response is silent with respect to the Claims 17-20.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al (US Pat. 5,525,494, June 1996) in view of Monforte et al. (US Pat. 5,700,642, December 1997) as applied to claims 3-12, 14-16 above, and further in view of Stratagene (Catalog 1988).

Neither Newton nor Monforte specifically teach packaging all of the necessary reagents into a kit.

However, Stratagene teaches reagent kits offer scientists good return on investment since only the quantities actually needed for the assay are premixed and

tested. Stratagene teaches kits save time and money because the kits already come prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Newton in view of Monforte with the teachings of Stratagene to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, solid support, chemicals for denaturing and other reagents of Newton and Monforte into a kit, as taught by Stratagene for the express purpose of saving time and money.

Response to Arguments

The response states that Claims 1-20 have been rejected as being anticipated by Newton et al., and other prior art, but does not address Urdea. The response provides no arguments directed to the kits of Claims 17-20. Applicants have asserts that they believe the rejections have been obviated and that claims 1-16 are believed to be allowable. However, the response is silent with respect to the Claims 17-20.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

New Matter

7. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "within 3 bases" are included. The amendment appears to be in response the the rejection under 112/2 with repsect to the indefiniteness of the relative term "near". However, the specification does not describe or discuses "a nucleotide within 3 bases of the 3' end of the primer". Instead the specification describes the "approach capitalizes on the lack of a 5' editing function in Taq polymerase; the DNA polymerase most often used in the PCR. The absence of this enzymatic function enables a nucleotide mismatch at or near the 3' end of a primer to prevent extension of that primer, and the failure to form a PCR product" (pg 4, lines 24-28). This description does not "within 3 bases". The concept of "within three bases" does not appear to be part of the originally filed invention. Therefore, "within 3 bases" constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

8. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A1) Claims 1-16 are rejected because it is unclear whether the newly added recitation with respect to step b of Claim 1 is intended to mean that the primer would not hybridize if the base is not present or whether the base at or within 3 bases of the primer 3' end will not hybridize. What the phrase "and will not hybridize if the base is not present" is unclear as to what it is referring back to. The interpretation that the primer will not hybridize if the base is not present does not appear to be part of the originally filed specification.

B1) Claims 1-16 are rejected as unclear whether the recitation "whether inherited or not inherited" is an artifact from the previous claims or whether this recitation is referring to the possibility that the DNA is inherited or not inherited. The specification does not appear to discuss this aspect.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 2, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Newton et al (US Pat. 5,525,494, June 1996).

Newton et al. (herein referred to as Newton) teaches a method for testing genomic DNA for a condition by making a solution comprising genomic DNA, adding a

primer which hybridizes to a targeted section of the genomic DNA, wherein a base at or near the primer 3' end may not hybridize to the genomic DNA, mixing DNA polymerase into the solution, amplifying the genomic DNA if the base at the 3' end of the primer hybridizes, capturing the amplified polynucleotide strand, detecting the amplified polynucleotide and finally determining a condition. Specifically, Newton teaches ARMS uses primers that allow amplification in an allele specific manner such that amplification is inhibited when the 3' terminal base of the primer is mismatched (col. 4, lines 45-50). ARMS may be used and captured on a single solid phase (col. 4, lines 55-60). Noewton teaches that both ARMS signal primers are labeled with a different fluorophore such as rhodamine. The two colors, namely red and green and their combination of yellow, allow detection of all normal and variant heterozygotes and homozygotes. Newton teaches capturing the polynucleotides on a solid support which contains probes sequences to hybridize to amplified products. Two different solids phases are described by Newton such that one of the phases is specific to the variant nucleic acid and the other is specific to the normal nucleic acid (col. 4-5)(limitations of Claim 1e and 13e). Newton teaches that the capture on solid phases is particularly useful in respect of dipstick type assay formats (col. 5, lines 14-15). As provided in Example 5, the specific capture and detection of amplification products based on the S locus of the alpha-1 antitrypsin gene (col. 24, lines 56-60). Oligonucleotides are immobilized to microtitre dishes (col. 26, lines 55-65)(limitations of Claim 7). ARMS analysis is performed using DNA, ARMS primer, and Taq polymerase (col. 27, lines 15-25)(limitations of Claims 1 and 13). The extension is analyzed on agarose gel and by solid phase capture and

detection (col. 27)(limitations of Claim 2). An oligonucleotide conjugated to alkaline phosphatase is used for detection and for "clear diagnosis that the DNA is from a homozygous S variant of alpha-1 antitrypsin (col. 28)(limitations of Claim 6, 8, 9, 10). Following hybridization, the wells were washed using 2xSSC (col. 24, lines 25-38). Finally, a color development solution comprising alkaline phosphatase and BCIP was added to the solution for visualization (col. 34).

Response to Arguments

The response traverses the rejection. The response asserts that Newton does not teach the two selective hybridization steps. This argument has been reviewed but is not convincing because Newton does teach the extension and the capture steps of the instant claims (see Col. 28-29). Example 5 is directed to this embodiment. Example 5 is an example for the specific capture and detection of amplification products. Solid phase capture and detection of ARMS products is described in column 28. PCR products from the S normal primer tube and the PCR product from the S variant primer tube were added to different well within the microtiter plate and allowed to hybridize. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al (US Pat. 5,525,494, June 1996) in view of Monforte et al. (US Pat. 5,700,642, December 1997).

Newton et al. (herein referred to as Newton) teaches a method for testing genomic DNA for a condition by making a solution comprising genomic DNA, adding a primer which hybridizes to a targeted section of the genomic DNA, wherein a base at or near the primer 3' end may not hybridize to the genomic DNA, mixing DNA polymerase into the solution, amplifying the genomic DNA if the base at the 3' end of the primer hybridizes, capturing the amplified polynucleotide strand, detecting the amplified polynucleotide and finally determining a condition. Specifically, Newton teaches ARMS uses primers that allow amplification in an allele specific manner such that amplification is inhibited when the 3' terminal base of the primer is mismatched (col. 4, lines 45-50). ARMS may be used and captured on a single solid phase (col. 4, lines 55-60). Noewton teaches that both ARMS signal primers are labeled with a different fluorophore such as rhodamine. The two colors, namely red and green and their combination of yellow, allow detection of all normal and variant heterozygotes and homozygotes. Newton teaches capturing the polynucleotides on a solid support which contains probes sequences to hybridize to amplified products. Two different solids phases are described by Newton such that one of the phases is specific to the variant nucleic acid and the other is specific to the normal nucleic acid (col. 4-5)(limitations of Claim 1e and 13e). Newton teaches that the capture on solid phases is particularly useful in respect of dipstick type assay formats (col. 5, lines 14-15). As provided in Example 5, the specific

capture and detection of amplification products based on the S locus of the alpha-1 antitrypsin gene (col. 24, lines 56-60). Oligonucleotides are immobilized to microtitre dishes (col. 26, lines 55-65)(limitations of Claim 7). ARMS analysis is performed using DNA, ARMS primer, and Taq polymerase (col. 27, lines 15-25)(limitations of Claims 1 and 13). The extension is analyzed on agarose gel and by solid phase capture and detection (col. 27)(limitations of Claim 2). An oligonucleotide conjugated to alkaline phosphatase is used for detection and for "clear diagnosis that the DNA is from a homozygous S variant of alpha-1 antitrypsin (col. 28)(limitations of Claim 6, 8, 9, 10). Following hybridization, the wells were washed using 2xSSC (col. 24, lines 25-38). Finally, a color development solution comprising alkaline phosphatase and BCIP was added to the solution for visualization (col. 34).

Newton does not specifically teaches denaturing the amplified polynucleotides to form single-stranded polynucleotides prior to hybridization on a solid support.

However, Monforte teaches that primer extension products are routinely denatured from the target, using heat or chemical denaturant. Monforte also teaches "coupling of an oligonucleotide to a solid support may be carried out through a variety of immobilization attachment functional groups" (col. 17, lines 39-45). This includes biotinylated oligonucleotides which is the immobilized by attachment to a streptavidin-coated support (col. 19, lines 54-66).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Newton for ARMS primer extension on a solid support with the teachings of Monforte that

denaturing the extension product is routine in the art prior to subsequent hybridization to a solid support. The skilled artisan would have been motivated to have denatured the primer extension product of Newton with either chemical or heat denaturation methods for the expected benefit of obtaining suitable nucleic acid for further hybridization analysis.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the solid support attachment method of Newton with the equivalent as taught by Monforte. The skilled artisan would have recognized by the extensive teachings of Monforte that oligonucleotides may be linked to solid supports using numerous means. The utilization of a streptavidin/biotin was one equivalent means for attaching oligonucleotides to a solid support.

Response to Arguments

The response traverses the rejection. The response asserts that Newton does not teach the two selective hybridization steps. This argument has been reviewed but is not convincing because Newton does teach the extension and the capture steps of the instant claims (see Col. 28-29). Example 5 is directed to this embodiment. Example 5 is an example for the specific capture and detection of amplification products. Solid phase capture and detection of ARMS products is described in column 28. PCR products from the S normal primer tube and the PCR product from the S variant primer tube were added to different well within the microtiter plate and allowed to hybridize. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

11. No claims allowable over the art.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
July 27, 2001 jg

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800 1600